This Page Is Inserted by IFW Operations and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents will not correct images, please do not report the images to the Image Problem Mailbox.

We Claim:

10

15

1. A novel pyrrolo[2,1-c][1,4]benzodiazepine of formula IX where n is 3 to 10.

5 2. A novel pyrrolobenzodiazepine as claimed in claim 1 of the structure

3. A novel pyrrolobenzodiazepine as claimed in claim 1 of the structure

4. A novel pyrrolobenzodiazepine as claimed in claim 1 of the structure

5. A novel pyrrolobenzodiazepine as claimed in claim 1 of the structure

6. A novel pyrrolobenzodiazepine as claimed in claim 1 of the structure

20 7. A novel pyrrolobenzodiazepine as claimed in claim 1 of the structure

5

15

20

8. A novel pyrrolobenzodiazepine as claimed in claim 1 of the structure

9. A novel pyrrolobenzodiazepine as claimed in claim 1 of the structure

10. A process for the preparation of bis 2-fluoro pyrrolo[2,1-c][1,4]benzodiazepines of formula IX

Formula IX

where n is 3 to 10, which comprises:

- (a) reacting methyl (2S)-N-[4-benzyloxy-5-methoxy-2-nitrobenzoyl]-4-hydroxypyrrolidine-2-carboxylate dissolved in an organic solvent,
- (b) cooling the solution and adding a solution of diethylaminosulfurtrifluoride (DAST) in an organic solvent drop wise;
- (c) isolating the methyl (2S)-N-[4-benzyloxy-5-methoxy-2-nitrobenzoyl]-4-fluoropyrrolidine-2-carboxylate with DIBAL-H formed in the presence of an organic solvent and cooling;
- (d) isolating methyl (2S)-N-[4-benzyloxy-5-methoxy-2-nitrobenzoyl]-4-fluoropyrrolidine-2-carboxaldehyde formed;
- (e) protecting methyl (2S)-N-[4-benzyloxy-5-methoxy-2-nitrobenzoyl]-4-fluoropyrrolidine-2-carboxaldehyde with EtSH in presence of an organic solvent;
- (f) isolating (2S)-N-[4-benzyloxy-5-methoxy-2-nitrobenzoyl]-4-fluoropyrrolidine-2-carboxaldehyde diethylthioacetal;

5

10

15

20

(g) reacting the (2S)-N-[4-benzyloxy-5-methoxy-2-nitrobenzoyl]-4-fluoropyrrolidine-2-carboxaldehyde diethylthioacetal with a debenzylating agent to obtain (2S)-N-[4-hydroxy - 5 - methoxy - 2 - nitrobenzoyl] - 4 - fluoropyrrolidine - 2 - carboxaldehyde - diethylthioacetal of formula VI,

Formula VI

(h) reacting (2S)-N-[4-hydroxy-5-methoxy-2-nitrobenzoyl]-4-fluoro-2-carboxaldehyde diethylthioacetal of formula VI with a dibromoalkane in an aprotic water miscible organic solvent and in the presence of a mild inorganic base up to refluxing temperature and isolating 1,1'-{[(alkane-1,N-diyl)dioxy}bis[(2-nitro-5-methoxy-1,4-phenylene) carbonyl] bis [4-fluoropyrrolidin-2-carboxaldehyde diethylthioacetal] of formula VII where n is 3-10

Formula VII

(i) reducing the compound of formula VII with SnCl₂ .2H₂O in presence of organic solvent up to a reflux temperature and isolating 1,1'-{[(alkane-1,N-diyl)dioxy}bis[(2-amino-5-methoxy-1,4-phenylene)carbonyl]]bis [4-fluoro-pyrrolidin-2-carboxaldehyde diethylthioacetal]] of formula VIII where n is 3-10

Formula VIII

(j) reacting the compound of formula VIII with a deprotecting agent to obtain bis 2-fluoro pyrrolo[2,1-c][1,4]benzodiazepines of formula IX wherein n is as stated above.

435/NF/03

15

20

30

- 11. A process as claimed in claim 10 wherein the organic solvent used in steps (a), (b) and (c) comprises CH₂Cl₂.
- 12. A process as claimed in claim 10 wherein in step (a) the solution is cooled to a temperature of -78°C.
- 5 13. A process as claimed in claim 10 wherein the drop wise addition in step (b) is carried out for a period of 40 min.
 - 14. A process as claimed in claim 10 wherein step (c) is carried out after 15 hours of step (b).
- 15. A process as claimed in claim 10 wherein the cooling in step (c) is done to a temperature of -78°C and for a period of 45 minutes.
 - 16. A process as claimed in claim 10 wherein step (e) is carried out in presence of an organic solvent and at room temperature.
 - 17. A process as claimed in claim 10 wherein the the (2S)-N-[4-hydroxy-5-methoxy-2-nitrobenzoyl]-4-fluoro-2-carboxaldehyde diethylthioacetal of formula VI is reacted with a dibromoalkane in an aprotic water miscible organic solvent selected from the group consisting of acetone, acetonitrile and DMF and in the presence of a mild inorganic base selected from the group consisting of K₂CO₃, CsCO₃ and BaCO₃.
 - 18. A process as claimed in claim 10 wherein step (h) is carried out for a period of about 48 hours.
 - 19. A process as claimed in claim 10 wherein the reduction in step (i) is carried out in the presence of an organic solvent comprising methanol.
 - 20. A process as claimed in claim 10 wherein the deprotecting agent comprises a combination of HgCl₂ and HgO in CH₃CN/H₂O.
- 25 21. A process for the preparation of bis 2-fluoro pyrrolo[2,1-c][1,4]benzodiazepines of formula IX

Formula IX

where n is 3 to 10, which comprises:

(a) (2S)-N-[4-hydroxy - 5 - methoxy - 2 - nitrobenzoyl] - 4 - fluoropyrrolidine - 2 - carboxaldehyde - diethylthioacetal of formula VI,

5

10

15

20

25

Formula VI

(b) reacting (2S)-N-[4-hydroxy-5-methoxy-2-nitrobenzoyl]-4-fluoro-2-carboxaldehyde diethylthioacetal of formula VI with a dibromoalkane in an aprotic water miscible organic solvent and in the presence of a mild inorganic base up to refluxing temperature and isolating 1,1'-{[(alkane-1,N-diyl)dioxy}bis[(2-nitro-5-methoxy-1,4-phenylene) carbonyl] bis [4-fluoropyrrolidin-2-carboxaldehyde diethylthioacetal] of formula VII where n is 3-10

Formula VII

(c) reducing the compound of formula VII with SnCl₂ .2H₂O in presence of organic solvent up to a reflux temperature and isolating 1,1'-{[(alkane-1,N-diyl)dioxy}bis[(2-amino-5-methoxy-1,4-phenylene)carbonyl]]bis [4-fluoro-pyrrolidin-2-carboxaldehyde diethylthioacetal]] of formula VIII where n is 3-10

Formula VIII

- (d) reacting the compound of formula VIII with a deprotecting agent to obtain bis 2-fluoro pyrrolo[2,1-c][1,4]benzodiazepines of formula IX wherein n is as stated above.
- 22. A process as claimed in claim 21 wherein the (25)-N-[4-hydroxy-5-methoxy-2-nitrobenzoyl]-4-fluoro-2-carboxaldehyde diethylthioacetal of formula VI is reacted with a dibromoalkane in an aprotic water miscible organic solvent selected from the group consisting of acetone, acetonitrile and DMF and in the

435/NF/03

- presence of a mild inorganic base selected from the group consisting of K_2CO_3 , $CsCO_3$ and $BaCO_3$.
- 23. A process as claimed in claim 21 wherein step (b) is carried out for a period of about 48 hours.
- 5 24. A process as claimed in claim 21 wherein the reduction in step (c) is carried out
 / in the presence of an organic solvent comprising methanol.
 - 25. A process as claimed in claim 21 wherein the deprotecting agent comprises a combination of HgCl₂ and HgO in CH₃CN/H₂O.
- 26. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound of formula IX and pharmaceutically acceptable additives.
 - 27. Method for the treatment of cancer in a patient suffering from the same, said method comprising administering to the patient a pharmaceutically effective amount of a compound of formula IX.
 - 28. A method as claimed in claim 27 wherein the patient is a mammal.
- 15 29. A method as claimed in claim 27 wherein the mammal is a human being.
 - 30. A method as claimed in claim 27 wherein the cancer is selected from the group consisting of leukemia, non-small cell, lung, colon, CNS, melanoma, ovarian, renal, prostate and breast.
- 31. Use of a compound of formula IX for the treatment of cancer selected from the group consisting of leukemia, non-small cell, lung, colon, CNS, melanoma, ovarian, renal, prostate and breast in a subject suffering from the same.

25

30